PAPER

Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease

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Background: An inverse relation exists between smoking and coffee intake and Parkinson's disease (PD). The present study explored whether this is explained by low sensation seeking, a personality trait believed to characterise PD.
Methods: A total of 106 non-demented patients with PD and 106 age and sex matched healthy controls completed a short version of Zuckerman's Sensation Seeking Scale (SSS), the Geriatric Depression Scale, and the Trait Anxiety Inventory. Data were collected on past and current cigarette smoking, and participants also completed food frequency questionnaires to estimate current caffeine and alcohol intake.
Results: Patients with PD had lower sensation seeking and higher depression and anxiety scores. They were also less likely to have ever smoked, and had lower caffeine and alcohol intakes. Analysis of the data using conditional logistic regression suggested that the inverse association of PD risk with sensation seeking was independent of smoking, and caffeine and alcohol intake. Moreover, low sensation seeking explained some of the apparent effect of caffeine and alcohol intake on PD. However, the effect of smoking was weakened only slightly when SSS was included in the regression model.
Conclusion: This study raises the possibility that there is a neurobiological link between low sensation seeking traits—which might underlie the parkinsonian personality—and the hypothetical protective effect of cigarette smoking and caffeine consumption on PD.

Parkinson's disease (PD) is strongly linked to advancing age and mildly linked to male sex but the aetiology of the illness is obscure. Epidemiological studies have consistently demonstrated a robust inverse relation between smoking and the subsequent risk of PD. Three recent meta-analyses of case–control and cohort studies have examined the association between smoking and PD.[1–3] Compared with never-smokers, the pooled relative risk of PD for ever-smokers was 0.51–0.59, for past smokers 0.66–0.80, and for current smokers 0.35–0.39. PD risk also decreases with cumulative exposure to smoking: the relative risk per 10 additional pack years was between 0.78 and 0.84. This relation has been claimed to exist even after adjusting for possible genetic influences on addictive behaviours.[2] Caffeine intake also appears to be protective against PD independently of smoking.[2] A meta-analysis showed a pooled relative risk of PD of 0.69 (95% CI 0.59 to 0.80) for coffee drinkers compared with non-coffee drinkers.[2] An independent predictive relation between alcohol intake and PD is less clear[4] and transient parkinsonism has even been described after alcohol withdrawal and excess.[5] A possible explanation is that the central actions of caffeine and nicotine may improve the health of the brain dopamine system[1] and protect against PD.[6]

However, it is possible that these findings are epiphenomena rather than being causally linked. Certain personality characteristics of individuals destined to develop PD may make them less prone to start smoking (and/or more likely to stop).[7] Certain genes such as polymorphisms in genes involved in dopamine catabolism[8] may also modify behaviours such as smoking, and caffeine and alcohol intake.

Individual differences in impulsive sensation seeking (ISS) traits are argued to reflect partly heritable variations in activity of nucleus accumbens related and cortical brain dopamine systems.[9] Individuals who score highly on ISS inventories exhibit risky, sensation seeking behaviours, and in children, ISS traits predict the uptake of smoking[10] and experimentation with alcohol.[11] In adults there is a strong relation between sensation seeking and continued smoking[12] and alcohol misuse.[13] Caffeine intake is also related to sensation seeking, as is the intake of other bitter substances—for example, tea.[11]

Patients with PD show reduced scores on ISS inventories and are less likely to engage in sensation seeking behaviour.[14] Personality characteristics at the lower pole of the ISS dimension (that is, conscientiousness, anhedonia, low aggressivity, and attitudinal inflexibility) may precede the onset of overt clinical symptoms in PD by several years.[15] Mood disturbance is integrally linked to PD[16] and ISS traits may also mediate a heritable susceptibility to the development of depression and anxiety.[17] Much case–control research has explored the extent to which smoking, and caffeine and alcohol intake independently affect PD risk. We sought to investigate the relation between these behaviours and PD risk and specifically whether ISS traits might significantly influence this relation.

METHODS

Patients

Consecutive outpatients of Caucasian descent fulfilling Queen Square Brain Bank criteria for PD[18] underwent a Mini-Mental State Examination[19] (MMSE) administered by the examining physician and were invited to participate if the MMSE score was ⩾26. We excluded patients with significant cognitive decline because of the requirement to complete the behavioural and depression rating scales. The Unified Parkinson's Disease Rating Scale (UPDRS)[20] part II was rated

Abbreviations: GDS, Geriatric Depression Scale; ISS, impulsive sensation seeking; PD, Parkinson's disease; SSS, sensation seeking scale; TAI, Trait Anxiety Inventory

for the ''on'' state and patients provided a list of all current medications and their dosages. Demographic data including age, sex, and age at onset of symptoms of PD were also collected. Similar to previous reports, we calculated the daily L-dopa equivalent unit (LEU) dose for each patient.[21] In the recruitment period, 167 PD patients were identified; 29 patients were ineligible due to the presence of significant cognitive decline (that is, MMSE<26), and 32 did not consent or did not return the questionnaire. The 106 PD patients participating had a mean age 65.3 years (range 38–81) and 65 were men.

Controls

Each case was individually matched by age (±2 years) and sex to a control participant. In the same period, 42 suitable partners or friends of participating patients without PD or dementia attending the outpatient department and 22 outpatients with minimally disabling dystonia or hemifacial spasm agreed to participate. If agreeable, the participants underwent an MMSE and completed consent procedures. Twenty-two control participants either did not consent or did not return the questionnaire. The remaining controls (n = 42), of Caucasian descent, were recruited at random from the Medical Research Council Cognition and Brain Sciences Unit healthy volunteer panel. The 106 controls had a mean age of 65.3 years (range 39–82) and 65 were men.

Questionnaires

Participants who provided written informed consent to protocols approved by the local ethics committee were given a series of questionnaires to complete in their own time and return them in a reply-paid envelope. The questionnaires included a short version of the sensation seeking scale[11 22] (SSS), the Trait Anxiety Inventory[23] (TAI), and Geriatric Depression Scale[24] (GDS). Data were collected on present and past cigarette smoking, number of cigarettes smoked, age of starting to smoke, and pipe and cigar smoking.[25]

We assessed the consumption of regular coffee, tea, chocolate milk, caffeinated soft drinks, and chocolate with a semiquantitative food frequency questionnaire based on those used in previous reports.[4 26] The reproducibility and validity of related questionnaires have been established for both alcohol[27] and caffeine[28] intake. A commonly used portion size was specified for each beverage, and the participants were asked how often on average over the past month they had consumed the equivalent amount. Seven possible response categories ranged from ''never or rarely'' to ''six or more times per day''. Caffeine intake was estimated by multiplying the daily consumption frequency of each category by its estimated caffeine content and was converted into the number of ''standard'' coffees with the formula: caffeine (mg/day)/120. The content of caffeine for each portion was assumed to be as follows: caffeinated soft drink 45mg/can, coffee 120 mg/cup, decaffeinated coffee 5 mg/cup, tea 47 mg/cup, chocolate milk 8 mg/cup, and 50 g chocolate bar 10 mg. Alcohol beverage sizes were pints for beers, 150 ml per glass of wine, and a standard measure of liquor. The estimated alcohol content (in grams) was: low alcohol beer 6, beer 18, wine 12, and liquor 14. The weekly intake in alcohol units (where a unit of alcohol was 8 g) was obtained by multiplying the weekly consumption frequency of each alcohol beverage by its estimated alcohol content.

Data analysis

We assessed the independent correlations between SSS and caffeine, alcohol and cigarette intake with Spearman's correlation coefficient (r_S). Baseline characteristics of the groups were compared with Wilcoxon's signed-rank tests. Continuous data for cigarette, caffeine, and alcohol exposure were grouped in categories to simplify interpretation of the estimated effects of each variable, facilitate model checking and improve model fit, and reduce the influence of extreme values, while attempting to maximise the number of separate categories. Cigarette exposure was grouped into six categories according to 10 pack year increments: category 1 = never-smoking, 2 = 0.1–10 pack years, 3 = 10.1–20 pack years, 4 = 20.1–30 pack years, 5 = 30.1–40 pack years, 6 = 50+ pack years. Caffeine intake was grouped into five categories representing 1 unit increases in daily consumption up to 5 units: category 1 = 0–0.9, 2 = 1–1.9, 3 = 2–2.9, 4 = 3–3.9, 5 = 4–4.9, 6 = 5+. Alcohol intake was grouped into three categories such that category 1 = no alcohol intake in the last week, 2 = 0.1–14 units in the last week, 3 = 14.1+ units in the last week. The variable sensation seeking score was dichotomised based upon the median score of control subjects (low SSS ⩽4; high SSS>4). Conditional logistic regression[29] was used to investigate the independent effect of each variable after adjusting for the effect of sensation seeking. Statistical analysis was performed with Stata Version 7.0 (Statacorp 2001).

The odds ratios (OR) are given with 95% confidence intervals in the results.

RESULTS

Across all participants, there was a strong correlation between the SSS score and caffeine intake ($r_S = 0.153$, $p = 0.026$), alcohol intake ($r_S = 0.345$, $p<0.001$), and cigarette pack/years exposure ($r_S = 0.181$, $p = 0.008$). There was no significant correlation between depression or anxiety and smoking, or caffeine or alcohol intake (data not shown). Table 1 shows that the PD patients had significantly lower SSS scores and heightened depression scores relative to controls. In the PD patient group, SSS correlated inversely with GDS ($r_S = -0.310$, $p = 0.002$) and TAI ($r_S = -0.242$, $p = 0.025$) but not with the UPDRS part II or disease duration. SSS also significantly inversely correlated with GDS ($r_S = -0.276$, $p = 0.006$) and TAI ($r_S = -0.326$, $p = 0.001$) in controls.

Smoking, caffeine, and alcohol behaviours

Table 2 shows smoking, and caffeine and alcohol intake in the PD patients and controls. All smokers among the controls and all except one smoker among the patients were cigarette smokers. There was no significant difference in age of onset of smoking or the maximum number of cigarettes smoked per day between cases and controls. Duration of smoking, however, was significantly shorter in cases compared with controls. The PD patients stopped smoking a mean (SD) 16.2 (13.9) years prior to onset of symptoms and there was a

Table 1 Individual characteristics of patients with Parkinson's disease (PD) and controls in the present study. Values are mean (range)

	PD	Controls	p value
Number	106	106	
Mini-Mental State Examination	28.8 (26–30)	29.5 (26–30)*	0.009
Disease duration	11.1 (2–40)	–	
UPDRS part II	14.7 (3–37)	–	
L-dopa equivalent unit	852 (0–3200)	–	
Sensation Seeking Scale	3.0 (0–8)	3.9 (0–12)	0.002
Geriatric Depression Scale	11.5 (0–30)†	6.8 (0–28)	<0.001
Spielberger Trait Anxiety Inventory	42.8 (21–63)‡	35.7 (22–68)	<0.001

Missing cases <2.9% unless otherwise stated.
*n = 52, †n = 99, ‡n = 86.
UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2 Smoking behaviours, and caffeine and alcohol consumption in patients with Parkinson's disease (PD) and controls

	PD*	Controls*	p value
Number	106	106	
Daily caffeine intake (units)	2.2 (1.5)	2.6 (1.4)	0.010
Weekly alcohol intake (units)	9.3 (15.2)	14.6 (19.6)	0.001
Age at onset of cigarette smoking (years)	19.5 (5.9)	17.8 (3.6)	0.459
Duration of cigarette smoking (years)	23.0 (13.5)	30.8 (14.6)	0.006
Maximum cigarettes/day smoked	17.7 (11.6)	19.0 (12.7)	0.626
	PD†	**Controls†**	**Odds of PD (95% CI)**
Cigarette smoking (pack/years)			
Never-smoker	62	46	1.35 (0.92 to 1.97)
0.1–10 pack years	17	14	1.21 (0.60 to 2.46)
10.1–20 pack years	8	10	0.80 (0.32 to 2.03)
20.1–30 pack years	9	14	0.64 (0.28 to 1.49)
30.1–40 pack years	5	7	0.71 (0.23 to 2.25)
40.1–50 pack years	4	15	0.33 (0.12 to 0.92)
Caffeine intake (units/day)			
0–0.9	22	11	2.00 (0.97 to 4.12)
1–1.9	33	25	1.32 (0.79 to 2.22)
2–2.9	27	31	0.87 (0.52 to 1.46)
3–3.9	10	16	0.63 (0.28 to 1.38)
4–4.9	8	15	0.53 (0.23 to 1.26)
⩾5	6	8	0.75 (0.26 to 2.16)
Alcohol intake (units/week)			
0	33	11	3.00 (0.34 to 0.98)
0.1–14	51	57	0.89 (0.62 to 1.31)
>14	22	38	0.58 (0.34 to 0.98)
Sensation seeking			
0–4	82	60	1.37 (0.98 to 1.91)
>4	24	46	0.52 (0.32 to 0.85)

*Values are mean (SD).
†Values are n (%).

significant correlation between age of PD symptom onset and age of smoking cessation ($r_s = 0.327$, $p = 0.037$). Age of PD onset in never-smokers was lower than ever-smokers (never-smokers mean 52.3 (10.6) years versus ever-smokers 56.7 (12.4) years, $p = 0.05$).

Higher cigarette consumption was associated with lower risk of PD (OR = 0.74 per 10 pack years (0.60 to 0.90), $p = 0.003$, pseudo $R^2 = 0.07$). Adding SSS to the model reduced the magnitude of the effect of cigarette consumption only slightly (that is, OR = 0.75 per 10 pack years (0.60 to 0.93), $p = 0.008$, pseudo $R^2 = 0.13$) only weakly suggesting that some of the apparent effect of cigarette smoking is also explained by the effect of SSS. Importantly, SSS was highly prognostic (OR = 0.40 (0.20 to 0.78), $p = 0.007$), independent of cigarette consumption. Higher caffeine consumption was also associated with lower risk of PD (OR = 0.74 per unit/day (0.60 to 0.92), $p = 0.007$, pseudo $R^2 = 0.05$). Adding SSS to the model reduced the magnitude of the effect of caffeine to OR = 0.79 per unit/day (0.63 to 0.99, $p = 0.036$, pseudo $R^2 = 0.10$). This finding suggests that some of the apparent effect of caffeine intake is explained by the effect of SSS. The effect of SSS was significant independently of caffeine intake (OR = 0.43 (0.22 to 0.82), $p = 0.011$). Higher alcohol consumption was also associated with lower risk of PD (OR = 0.38 per category (0.23 to 0.64), $p<0.001$, pseudo $R^2 = 0.12$). Adding SSS to the model reduced the magnitude of the effect of alcohol to OR = 0.44 per category (0.26 to 0.75, $p = 0.002$, pseudo $R^2 = 0.14$); suggesting that some of the apparent effect of alcohol intake is also explained by the effect of SSS. The effect of SSS was independent of alcohol intake (OR = 0.50 (0.25 to 0.99), $p = 0.046$).

DISCUSSION

We found a positive relation between low sensation seeking and PD. Brain dopamine systems have been proposed to mediate particular behavioural and personality traits in PD that sometimes precede the emergence of motor symptoms by decades. PD patients tend to be anhedonic, scrupulous, socially withdrawn, low aggressive, attitudinally inflexible, disinclined to take risks[15] and show reduced ISS traits compared with matched medical controls.[30] In PD, ISS traits have been found to relate to dopaminergic function within cortical and striatal brain systems.[31 32] One previous study in PD has found a similar link between smoking behaviour and an ISS related trait, novelty seeking.[7]

We also observed a positive relation between sensation seeking and smoking, caffeine, and alcohol intake. In healthy adults, the observed overlap of smoking, caffeine, and alcohol behaviours supports a common mechanism in their initiation and maintenance.[33] One potential biological explanation is that the rewarding effects of all three are known to be modulated by dopamine systems related to the nucleus accumbens.[34] ISS traits predict the taking up[11] and maintenance[12] of these behaviours and several lines of evidence also link ISS traits to brain dopamine system function[35] including insular cortex[36] and nucleus accumbens[37] in healthy volunteers.

Sensation seeking also appeared to independently predict PD after adjusting for each of smoking, and caffeine and alcohol intake. This raises the possibility that ISS traits may interact with smoking, and caffeine and alcohol intake behaviours and a biological vulnerability to PD. ISS traits may potentially interact with other behaviours that are linked to PD (fig 1). Low sensation seekers may also be more susceptible to environmental toxicants. Shyness is a low ISS trait that is found more frequently in first degree relatives of PD patients compared with controls[38] and predicts higher reported illness rates in response to xenobiotics, such as pesticides.[38] In discordant PD monozygotic twins, shyness has been found to be commoner in the affected sibling.[39]

Although these analyses support an effect of ISS traits on PD risk it does not necessarily prove a pattern of causation

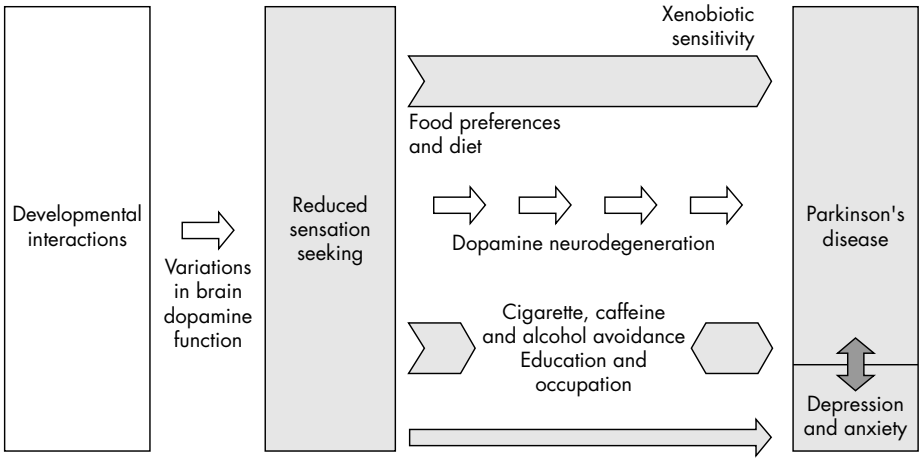

Figure 1 Schematic representation of the proposed interaction between reduced sensation seeking, behaviour, and environmental factors in PD risk.

and other interpretations of the data are possible. Sensation seeking scores may be reduced by the development of PD. Reduced sensation seeking may simply reflect disease involvement of mesocorticolimbic dopamine systems leading to a suppression of linked behaviours (that is, smoking, and caffeine and alcohol intake) in a protracted prodromal phase of PD. However, the capacity to generate normal synaptic dopamine levels in ventral striatal areas (that is, areas that mediate the ''rewarding'' effects of drugs) in patients with PD is relatively preserved even when dorsal striatal loss is severe,[40] making this less likely. Moreover, in the current sample, SSS scores did not relate to PD disease duration or severity.

We found that sensation seeking in both PD patients and controls was inversely correlated with depression. Low sensation seeking could contribute to a vulnerability state increasing the risk of concurrent depression in PD. Alternatively, depression, reduced ISS traits, and susceptibility to PD may all share a common neurobiological substrate. Depressed individuals (without PD) and individuals with anxiety disorders have reduced sensation seeking scores that do not vary with the degree of affect change during treatment of the mood state.[17] Sensation seeking is also negatively associated with familial susceptibility to depression[41] and individuals diagnosed as having depression in middle age have a higher risk of subsequently developing PD.[42] Finally, in the course of PD, depressive symptoms and anxiety are frequently seen but do not correlate well with indices of disease severity.[16]

The reduced sensation seeking model (fig 1) offers one possible explanation through which endogenously determined factors, such as individual variations in brain function, might interact with environmental exposures and lead to disease susceptibility.

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